# Articles

## Possible Interactions With Terfenadine or Astemizole

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**Concurrent use of terfenadine or astemizole with erythromycin or ketoconazole can prolong the QT interval and produce potentially fatal ventricular arrhythmias. We examine the frequency and patterns of concurrent prescribing and suggest methods to reduce the incidence of serious drug interactions. By retrospectively reviewing Oregon Medicaid prescription claims data over 22 months, we determined the frequency of concurrent prescribing of terfenadine or astemizole with macrolide antibiotics or ketoconazole. From 1991 to 1992, terfenadine use increased by 29%, with a seasonal peak in June of each year. Terfenadine was one of the most prescribed medications from March through July 1992. During the 22 months reviewed, there were 122 episodes of concurrent use of terfenadine or astemizole with macrolide antibiotics or ketoconazole. Most of these episodes (94%) involved terfenadine. The frequency of concurrent use increased more than threefold from 1991 to 1992. Although patients received prescriptions from different physicians in 48% of these episodes, they used different pharmacies only 3% of the time. We demonstrate that terfenadine use is extensive and increasing, thus increasing the possibility of serious interactions, and many physicians may remain unaware of this potential. Effective prospective screening by pharmacists could dramatically reduce the incidence of concurrent prescribing. Physicians must be aware of the potential for these drug interactions, avoid prescribing these medications concurrently, and consider these interactions in the evaluation of syncope and cardiac arrhythmias.**

(Zechnich AD, Hedges JR, Eiselt-Proteau D, Haxby D: Possible interactions with terfenadine or astemizole. West J Med 1994; 160:321-325)

Terfenadine (Seldane, Marion Merrell Dow) is a widely used nonsedating antihistamine approved for use in the United States in 1985 and taken by more than 100 million patients worldwide for symptoms of allergic rhinitis ("Dear Doctor Letter," Marion Merrell Dow Inc, August 6, 1990). Terfenadine was the tenth most prescribed medication in the United States in 1992.[1] Prolongation of the QT interval and serious ventricular arrhythmias (torsades de pointes) leading to syncope, cardiac arrest, or sudden death have increasingly been reported when terfenadine or astemizole (Hismanal, Janssen Pharmaceutica) is taken concomitantly with erythromycin or ketoconazole (Marion Merrell Dow Inc, oral communication, January 1993).[2,3] Case reports have detailed substantial interactions when terfenadine is used at recommended doses concomitantly with ketoconazole[2,3] or in patients with hepatic dysfunction[4] or acute or chronic overdose,[5-8] and recent clinical trials have confirmed the potential for prolonging the QT interval.[9] As of May 1992, about 80 serious cardiovascular events were reported to the manufacturer,[10] including cases of terfenadine overdoses and interactions with erythromycin, ketoconazole, and troleandomycin. The occurrence of notable interactions is probably underrecognized and underreported, however.

Similar adverse events have been reported with the use of astemizole, a similar nonsedating $H_1$-antagonist. Ventricular arrhythmias due to prolonging of the QT interval have been reported with astemizole use of 10 to 20 mg per day[11,12] and in patients with acute overdose,[13-16] and the manufacturer has made concurrent use with erythromycin, ketoconazole, or itraconazole a contraindication to astemizole therapy. Janssen notified prescribers of these adverse effects in July 1992 and announced the contraindications in a separate mailing in the fall of 1992 ("Dear Health Care Professional," Janssen Pharmaceutica, Oct 26, 1992).

Because of the serious nature of these interactions, considerable efforts have been made to inform health care

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This investigation was supported in part by National Library of Medicine Informatics Training Grant 1T15LM07088.

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**ABBREVIATIONS USED IN TEXT**

FDA = Food and Drug Administration
OMAP = Office of Medical Assistance Programs

professionals, but there is still concern that many providers remain unaware of the potential for serious sequelae. In 1990, Marion Merrell Dow Inc, issued a letter to 300,000 physicians and pharmacists reporting the possible consequences of interactions of terfenadine with ketoconazole or macrolide antibiotics ("Dear Doctor Letter," Marion Merrell Dow Inc, Aug 6, 1990). In addition to published case reports, these warnings were repeated in the *FDA Medical Bulletin* and *Drug Interactions Newsletter.*[17,18] Because it was apparent that concurrent prescribing of these medications continued (Marion Merrell Dow Inc, written communication, October 1992), the FDA issued a press statement on July 6, 1992, using national media coverage to announce the contraindication to concomitant use with erythromycin or ketoconazole. Since then, the FDA has reiterated the warnings in September 1992,[19] and the manufacturer has sent another 1.6 million letters to physicians and pharmacists in two separate mailings (Marion Merrell Dow Inc, oral communication, October 1992). The effectiveness of these measures has not been studied, and the magnitude of the problem of concurrent prescribing has not yet been reported.

The purpose of this investigation is to determine the incidence of concurrent prescribing of terfenadine or astemizole with macrolide antibiotics or ketoconazole and to examine possible methods to reduce the frequency of such interactions.

## Methods

We retrospectively reviewed prescription claims under Oregon's Medicaid program between January 1991 and October 1992, which enabled us to ascertain the number of terfenadine and astemizole tablets prescribed and the number of episodes of concurrent use with contraindicated medications. To identify episodes of concurrent use, patients who received terfenadine or astemizole along with erythromycin, ketoconazole, or troleandomycin were selected by database query. The query analyzed prescription claims between January 1991 and mid-September 1992 and selected only patients who received both medications within 45 days of each other. For each of these patients, a profile was generated that included the date of dispensing, strength and quantity of tablets, prescriber, and dispensing pharmacy for all medications funded by Oregon Medicaid during the study period. One physician and two pharmacists reviewed these profiles independently to identify any concomitant use of these medications. An episode of concurrent use was defined as the prescription of a macrolide antibiotic (erythromycin or troleandomycin) or ketoconazole for a patient currently using terfenadine or astemizole, or vice versa. For the purposes of this investigation, any overlap of one or more days was considered important. The duration of therapy was calculated by the number of tablets prescribed, assuming the medication was prescribed at recommended doses. Although most episodes of concurrent use were independent pairs of prescriptions, any new prescription with the potential for interaction was regarded as a separate episode—that is, a patient receiving two erythromycin prescriptions during a single course of terfenadine was recorded as having two episodes of concurrent use. After the three reviewers reached consensus, data were transferred into a microcomputer database for analysis.

The Office of Medical Assistance Programs (OMAP) provides medical coverage for more than 220,000 Oregonians. Most of these patients—about 68%—are women.[20] A total of 10,000 to 12,000 health care professionals currently care for Medicaid patients, including 5,729 physicians (located both in and out of Oregon) and 1,349 dentists. Based on January 1992 data, there are 581 nonhospital pharmacies licensed by the Board of Pharmacy in Oregon. To receive reimbursement from OMAP for dispensed medications, pharmacists must submit a claim for each prescription dispensed under Medicaid funding. In 1991, approximately 2.5 million prescriptions were filled under this program in the state of Oregon. An information management company maintains the database of statewide prescription claims and responds to requests for information.

## Results

### *Terfenadine and Astemizole Prescribing*

Terfenadine was one of the top ten medications prescribed in our population during the months of March through July 1992, ranked by number of prescriptions per month categorized by the National Drug Code; in June 1992, it was the most prescribed medication by the National Drug Code. In our population, 542,563 terfenadine tablets (average, 45,214 tablets per month) were dispensed in 1991. The greatest usage was in June 1991 (61,147 tablets). In 1992, the number of terfenadine prescriptions increased: 593,863 tablets were dispensed between January and October (59,386 tablets per month). Figure 1 shows the seasonal increase in terfenadine use and the 29% overall increase from 1991 to 1992 (average monthly us-

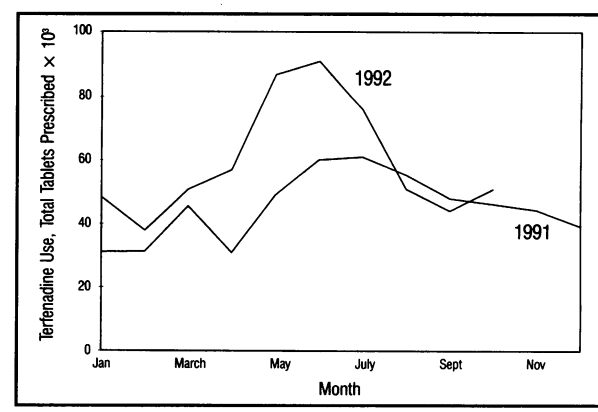


**Figure 1.**—The graph shows the number of tablets of terfenadine prescribed for patients covered by the Oregon Medicaid program between January 1991 and mid-September 1992.

age between January and October of each year). The most dramatic increases occurred in April and May, in which terfenadine use increased 85% and 77%, respectively, compared with the same months in 1991. Astemizole use demonstrated a similar seasonal pattern, with a total of 124,116 tablets prescribed between February and October 1992.

*Concurrent Use*

A review of prescription claims revealed 122 episodes of concurrent use of terfenadine or astemizole with a macrolide antibiotic or ketoconazole during the study period in Oregon's Medicaid population. Of these episodes, 115 involved terfenadine (94%) and 7 involved astemizole (6%). Of the 122 concurrent episodes, 29 occurred in 1991 and 93 occurred in 1992 (a 3.2-fold increase, Figure 2); 96 of 122 (79%) involved concomitant use with erythromycin, 13 (11%) with ketoconazole, and 13 (11%) involved troleandomycin. Although patients received prescriptions from two different physicians in 48% of these episodes, they used different pharmacies to fill the prescriptions only 3% of the time. In 29 (25%) of these episodes involving terfenadine, both prescriptions were dispensed on the same day. Of the 115 episodes, 22 involving terfenadine occurred after the FDA's media coverage of the contraindication on July 6, 1992. The mean number of days of overlap between concurrent prescriptions was 9.98 days. In four episodes (3%), the overlap was only one day. Concurrent use with metronidazole was incidentally noted in three of the study patients.

*Prescribers*

There were 69 different health care professionals who prescribed medications in these episodes of concurrent use, including 19 family practitioners, 12 internists, 6 general practitioners, 6 pediatricians, 5 internal medicine subspecialists, 4 dermatologists, 3 dentists, 3 allergists, 3 emergency physicians, 3 head and neck surgeons, 2 gynecologists, 1 general surgeon, 1 neurologist, and 1 whose specialty was unknown. Primary care physicians accounted for 59% of the prescribers involved in these episodes. No specific geographic pattern could be recognized. Distribution among rural and urban settings approximated the distribution of physicians in the state of Oregon.

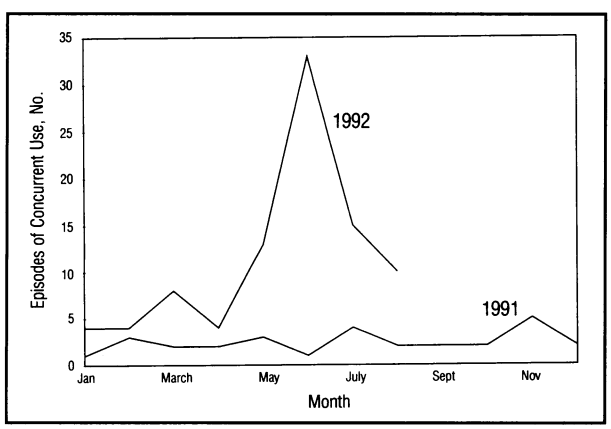


**Figure 2.**—The graph shows the number of episodes of concurrent use of terfenadine or astemizole with a macrolide antibiotic or ketoconazole in Oregon's Medicaid population from January 1991 through September 1992.

*Pharmacies*

In all, 38 different pharmacies dispensed medications involved in these episodes.

*Patients*

There were 40 different patients who received concurrent therapy. The average age of these patients was 40 years (range, 6 to 77), and 33 (82%) were women. The number of episodes of concurrent use per patient ranged from 1 to 24 (mean 3.0, mode 1, median 1). (The patient involved in 24 episodes was being treated long term with erythromycin by a dermatologist while receiving intermittent terfenadine therapy from two different otolaryngologists and a family practitioner.) The number of patients receiving concurrent prescriptions increased 4.75-fold from 1991 to 1992: 8 different patients in 1991 (average, 3.6 episodes per patient) and 38 different patients in 1992 (average, 2.4 episodes per patient). Many of these patients appeared to receive maintenance therapy with terfenadine as 20 of 40 patients received 200 or more tablets between January and September 1992, and 8 patients received 400 or more tablets (200 days of treatment) in this 273-day time period.

## Discussion

This investigation found that terfenadine and astemizole use is widespread and increasing rapidly. Between March and July 1992, terfenadine ranked in the top ten medications prescribed in our population, as ranked by the National Drug Code; terfenadine prescription costs totaled $938,236 over the study period. Terfenadine use follows a seasonal pattern with heaviest use in May and June, and this seasonal variation was even more pronounced in 1992 (Figure 1). The number of terfenadine tablets dispensed per month increased 29% in 1992 compared with the same ten-month period of 1991, and the number of tablets dispensed in the month of May rose 77% over that of the previous year. This widespread use increases the number of patients at risk for possible interactions with other commonly prescribed medications such as erythromycin. Both terfenadine and astemizole are available without a prescription in Canada—although they are kept behind the counter and must be requested—and the FDA has considered over-the-counter availability in the United States.[21] Such action could dramatically increase the number of patients at risk.

The number of episodes of concurrent use of terfenadine with erythromycin or ketoconazole also increased markedly in 1992, as depicted in Figure 2. The number of episodes of concurrent use increased 3.2-fold from 1991 to 1992, and the number of patients involved in these episodes rose almost 5-fold, representing a pronounced increase in the number of patients at risk from these drug interactions. Because Oregon Medicaid covers about 9%

of the state's population, this study probably represents only a small fraction of patients receiving concurrent therapy in Oregon and a small proportion of those at risk nationwide.

Some physicians may remain unaware of the potential for interaction. In nearly half (52%) of the episodes of concurrent use, a single prescriber was responsible for both prescriptions. In 25% of the episodes, both medications were dispensed on the *same day.* Because this investigation examines prescription claims, the records reflect when a prescription is dispensed and not necessarily when a physician actually issued the prescription. In some of these episodes, the patient may have received a refill of a previously written prescription. A single primary provider should be aware of all medications currently taken by his or her patient, particularly when a new medication such as terfenadine or erythromycin is added.

How effective are "Dear Doctor" letters or national media coverage in informing physicians, changing their prescribing practices, and encouraging them to check their patients' medication profiles to prevent concurrent prescribing? Our investigation was not designed to measure whether physicians read the letters or incorporated the information into their practices, but our data suggest that informing physicians may have limited efficacy in preventing episodes of concurrent use. Despite considerable efforts to inform prescribers, concurrent use increased in Oregon. In 48% of these episodes, different physicians issued the medications. If a patient using terfenadine long term (as were many patients in our study) consulted a physician on an urgent, unscheduled basis, such as for bronchitis, that physician could issue erythromycin without having access to the patient's medical record. Even if an "informed" provider actively sought information about other medications, preventing concurrent use could rely on a patient's recollection of all of his or her current medications. Although educational efforts to alert physicians about possible interactions must be encouraged, the effectiveness of these efforts in preventing such interactions may be limited.

Recognizing pharmacists' responsibility to help prevent drug interactions, Congress included provisions in the Omnibus Budget Reconciliation Act of 1990 that require state Medicaid agencies to implement retrospective and prospective drug use review programs by January 1, 1993. These provisions specifically require that pharmacies screen at the point of sale for drug interactions, drug-disease contraindications, therapeutic duplication, incorrect dosage or duration of therapy, and drug-allergy interactions.[22] Most pharmacies use a computer system to monitor dispensing; as of mid-1991, 85.6% of 13,000 pharmacies responding to a survey indicated that they could screen electronically for drug interactions.[23] Few states have implemented a statewide system for such screening, however, and it remains uncertain how effectively possible interactions are detected by pharmacist review at the point of sale.

Our results strongly support an increased role for pharmacists in detecting possible drug interactions. Although patients received prescriptions from two different physicians in 48% of the concurrent use episodes, they used different pharmacies only 3% of the time. In other words, in 97% of these concurrent use episodes, the same pharmacy dispensed both medications involved in the possible interaction. As previously noted, both medications were dispensed on the same day in 25% of the episodes, presumably at the same time. Therefore, pharmacists have an excellent opportunity to reduce dramatically the potential for concurrent prescribing. Whereas most (85.6%) pharmacies report the capability to screen electronically for drug interactions,[23] our data suggest that some are not effectively detecting concurrent prescribing. With effective screening (prospective drug use review), as many as 97% of the episodes of concurrent use identified in this investigation might have been prevented.

Five patients were changed from terfenadine to astemizole just after the interactions with terfenadine received national media coverage. Although it has been less publicized, similar QT prolongation has been reported with astemizole use, and its manufacturer has also announced contraindications to concurrent use with macrolide antibiotics and ketoconazole.

The risk of adverse effects to a patient on concurrent therapy is difficult to estimate. Our investigation included four episodes in which the overlap in drug therapy was only one day, and the clinical importance of this degree of overlap remains unclear. In addition, there appears to be considerable interindividual variability in electrocardiographic changes with the accumulation of terfenadine.[9] Some prescribers may have elected to continue these medications in patients who had taken the combination previously without incident, although this practice should be discouraged. The lack of adverse effects from one episode of concurrent use does not guarantee safe concurrent therapy in the future. In any case, although the ultimate risk of adverse effects is difficult to quantitate in each episode of concurrent use, the frequency with which these medications were issued concomitantly remains disturbing.

Several weaknesses in this study should be acknowledged. First, our investigation measures only episodes of concurrent prescription and cannot assess the clinical consequences of these interactions. Second, by reviewing claims data, our investigation cannot determine how the medications were actually used by patients, but can only measure how they were dispensed. Some patients may have temporarily discontinued terfenadine use when issued a prescription for erythromycin, and others may have taken higher doses than recommended. Third, our study was not designed to estimate the effects of the most recent media coverage. Because the expected seasonal decline in antihistamine use occurred at the same time as the media release of the warnings, the incidence of concurrent prescribing in 1993 must be measured to estimate the relative effects of these two influences. Finally, complete data depend on the timely filing of claims by Oregon pharmacists, and the most recent data may be incomplete. Therefore, the incidence of concurrent prescribing in August and September 1992 is probably underestimated by our investigation.

**Acknowledgment**

Paul Gorman, MD, and Mark Helfand, MD, critiqued the manuscript of this article.

## REFERENCES

1. Simonsen LLP: Top 200 drugs of 1992—What are pharmacists dispensing most often? Pharm Times 1993 Apr, pp 29-44

2. Monahan BP, Ferguson CL, Killeavy ES, Lloyd BK, Troy J, Cantilena LR Jr: Torsades de pointes occurring in association with terfenadine use. JAMA 1990; 264:2788-2790

3. Zimmermann M, Duruz H, Guinand O, et al: Torsades de pointes after treatment with terfenadine and ketoconazole. Eur Heart J 1992; 13:1002-1003

4. Venturini E, Borghi E, Maurini V, Vecce R, Carnicelli A: Prolongation of the QT interval and hyperkinetic arrhythmia probably induced by the use of terfenadine in a patient with hepatic cirrhosis [Italian]. Recenti Prog Med 1992; 83:21-22 [Eng Abstr]

5. Davies AJ, Harindra V, McEwan A, Ghose RR: Cardiotoxic effect with convulsions in terfenadine overdose (Letter). Br Med J 1989; 298:325

6. Bastecký J, Kvasnička J, Vortel J, Tauchman M, Wasylivová V: Severe intoxication with antihistamines complicated by ventricular tachycardia [Czech]. Vnitr Lek 1990; 36:266-269 [Eng Abstr]

7. Guilbaud JC, Moin M, Sader R: A case of rhythm disorder during terfenadine poisoning [French]. Reanim Soins Intensifs Med Urgence 1991; 7:233-234

8. MacConnell TJ, Stanners AJ: Torsades de pointes complicating treatment with terfenadine (Letter). Br Med J 1991; 302:1469

9. Honig PK, Worthman DC, Zamani K, Conner DP, Mullin JC, Cantilena LR: Terfenadine-ketoconazole interaction: Pharmacokinetic and electrocardiographic consequences. JAMA 1993; 269:1513-1518

10. Terfenadine drug interactions. Drug Interact Newslett [special issue] 1992, pp 586-588

11. Simons FER, Kesselman MS, Giddins NG, Pelech AN, Simons KJ: Astemizole-induced torsades de pointes (Letter). Lancet 1988; 2:624

12. Snook J, Boothman-Burrell D, Watkins J, Colin-Jones D: Torsade de pointes ventricular tachycardia associated with astemizole overdose. Br J Clin Pract 1988; 42:257-259

13. Hoppu K, Tikanoja T, Tapanainen P, Remes M, Saarenpää-Heikkilä O, Kouvalainen K: Accidental astemizole overdose in young children. Lancet 1991; 338:538-540

14. Tobin JR, Doyle TP, Ackerman AD, Brenner JI: Astemizole-induced cardiac conduction disturbances in a child. JAMA 1991; 266:2737-2740

15. Craft TM: Torsade de pointes after astemizole overdose. Br Med J (Clin Res) 1986; 292:660

16. Wiley JF II, Gelber ML, Henretig FM, Wiley CC, Sandhu S, Loiselle J: Cardiotoxic effects of astemizole overdose in children. J Pediatr 1992; 120:799-802

17. Ketoconazole (Nizoral) interactions. Drug Interact Newslett 1991; 11:495

18. Labelling change to reflect drug interaction between terfenadine and ketoconazole. FDA Med Bull 1991; 21:4-5

19. New boxed warnings added for Seldane, Hismanal. FDA Med Bull 1992; 22:2

20. Demographic Report on Oregon's Medicaid Population. Arlington, Va, Health Information Design, March 1992

21. Safety of terfenadine and astemizole. Med Lett 1992; 34:9-10

22. Omnibus Budget Reconciliation Act of 1990, 42 USCA §1396r-8(g)(1)(A)

23. Feegel K, Smith MD: Counseling and cognitive services for Medicaid patients under OBRA-90. Pharm Times 1992; 58(suppl):1-9